Successful resolution of hyperammonemia following hematopoietic cell transplantation with directed treatment of *Ureaplasma parvum* infection.

Riley Graetz, M.D.^{1,2}

Robyn Meyer, M.D.^{1,2}

Kareem Shehab, M.D.^{1,2}

Emmanuel Katsanis, M.D.^{1,2,3}

Department of Pediatrics¹, Banner University Medical Center², University of Arizona Cancer Center³, Tucson, Arizona

Address all correspondence to: Emmanuel Katsanis, M.D., Department of Pediatrics, University of Arizona, 1501 N. Campbell Ave., PO Box 245073, Tucson, AZ 85724-5073; Tel.: (520) 626-7053; FAX: (520) 626-6986
katsanis@peds.arizona.edu.

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Abstract

Hyperammonemia following hematopoietic cell transplantation (HCT) has been characterized as idiopathic and is associated with a very high mortality. A causal relationship between *Ureaplasma* infection and hyperammonemia in immunocompromised lung transplant recipients has recently been described. We document the first case of hyperammonemia following HCT associated with *Ureaplasma parvum*. The initiation of appropriate antibiotics resulted in rapid resolution of hyperammonemic encephalopathy and eradication of the implicating organism.

Introduction

Hyperammonemia is a rare complication of chemotherapy or hematopoietic cell transplantation (HCT) but the etiology is often unclear. Idiopathic hyperammonemia (IHA) was first reported following chemotherapy by Watson *et al.* in 1985 and since then numerous additional cases have been described with a greater than 75% mortality¹⁻⁵. Davies *et al.* identified hyperammonemia in 12 of 2358 patients (0.5%) undergoing HCT, all of whom were 19 years or older, with 10 (83%) dying of progressive encephalopathy despite treatment with dialysis and/or ammonia-trapping agents⁶. Among these cases, 11/12 underwent allogeneic HCT and 10/12 had leukemia. Other case reports have documented occurrence of IHA following autologous HCT, umbilical cord blood transplant, HCT for malignant and non-malignant conditions, and in pediatric HCT recipients⁷⁻¹⁰. The typical presentation is that of a metabolic encephalopathy in an immunocompromised patient with lethargy, confusion, disorientation, agitation and/or combativeness, hyperventilation with respiratory alkalosis, seizures, coma and eventually death.

Bharat *et al.* recently described a causal relationship between *Ureaplasma* infection and hyperammonemia in immunocompromised lung transplant recipients¹¹⁻¹⁴. We describe the first case of hyperammonemia following HCT associated with *Ureaplasma parvum*. Initiation of appropriate antibiotic therapy resulted in prompt resolution of hyperammonemic encephalopathy and eradication of the causative organism.

Case Report

A 21-year-old male with AML in second remission underwent a matched unrelated donor peripheral blood HCT following busulfan, fludarabine melphalan and anti-thymocyte globulin (ATG) conditioning¹⁵. Graft-versus-host disease prophylaxis consisted of cyclosporine and methotrexate. He received a single dose of prophylactic levofloxacin 500mg for neutropenia on day 0 (HCT day) which was replaced by empiric antimicrobial therapy (vancomycin, cefepime and voriconazole) as he developed fever on day +1. All blood cultures proved negative. Influenza B was detected in the nasopharynx by RT-PCR on day +5, and he received a 5-day course of oseltamivir. He developed grade III mucositis but refused scheduled morphine. He was noted to have mild respiratory distress, requiring O₂ by nasal cannula. Chest radiograph revealed scattered opacities consistent with developing pneumonia. Cefepime was replaced by meropenem on day +8. On day +12 he began having acute mental status changes, including disorientation and inability to follow commands, but without focal neurological findings on exam. Computed tomography of the head was unremarkable. Laboratory investigations revealed a blood ammonia level of 130 μ Mol/L (normal 10-72) with a mildly elevated bilirubin of 2.9 and normal transaminase levels. He was started on rifaximin 550 mg BID, while parenteral nutrition and potentially hepatotoxic drugs were discontinued¹⁶. Over the next 8 hours he developed hyperventilation with respiratory alkalosis and became increasingly confused and agitated. He became unresponsive and was transferred to the intensive care unit, where he was intubated on arrival for airway protection and was mechanically ventilated on minimal settings. Repeat ammonia levels remained elevated (Figure 1), and lactulose 16.7g QID was started on day +13. Defibrotide was initiated on day +14 for suspicion of sinusoidal obstruction syndrome due to an increase of bilirubin

up to 6 mg/dl and mild coagulopathy (INR 1.4 and D-Dimer 5 µg/ml), but abdominal ultrasound did not reveal abnormal hepatic flow or ascites; defibrotide was discontinued after five days. On day +15 he developed an abnormal respiratory pattern consistent with brain stem dysfunction requiring escalation of mechanical ventilation. Later the same day while on route to magnetic resonance imaging (MRI), he had a generalized, tonic-clonic seizure lasting 16 minutes and requiring lorazepam, phenobarbital and levetiracetam. MRI showed bilateral diffuse cortical and subcortical restricted diffusion, thought to be post-ictal in nature. Continuous electroencephalogram failed to show epileptiform activity, and he had no further seizure activity while continuing on maintenance dosing of levetiracetam. On day +15 blood and tracheal aspirate samples were sent for *U. urealyticum* and *U. parvum* PCR and azithromycin 500 mg and levofloxacin 750 mg IV daily were added for empiric coverage. Within 24 hours of single doses of azithromycin and levofloxacin, ammonia levels normalized (Figure 1). The tracheal aspirate PCR was positive for *U. parvum* and negative for *U. urealyticum*; blood was negative for both organisms¹⁷. With improving mental status, the patient was extubated on day +18. Rifaximin and lactulose were discontinued on days +20 and +21 respectively. Repeat sputum sample on day +24 was negative for *U. parvum* by PCR. Azithromycin was discontinued on day +29 and levofloxacin on day +32. Monitoring of ammonia levels demonstrated a progressive increase and levofloxacin 750 mg daily was restarted for one week (day 45-52) resulting in a decrease in ammonia. Once again four days after discontinuing levofloxacin, ammonia levels increased above the normal range and the antibiotic was restarted on day 56 with an improvement in hyperammonemia and continued with ammonia levels remaining normal when last tested on day +80.

Discussion

There have been numerous reports and small case series of IHA following high-dose chemotherapy and/or HCT with dismal outcomes¹⁻¹⁰. The etiology of IHA has remained speculative and multifactorial. One putative mechanism includes increased catabolism from chemotherapy, steroids or infection, in the setting of increased nitrogen load from parenteral nutrition and gastrointestinal bleeding, overwhelming urea synthesis and resulting in excessive ammonia production⁶. Others have suggested that urea-splitting bacteria producing urease may contribute to hyperammonemia¹⁸. Additional reports have indicated that acquired deficiency of hepatic glutamine synthetase or urea cycle disorders may lead to hyperammonemia in transplant recipients¹⁹⁻²¹. *Ureaplasma* species are dependent on hydrolysis of urea to ammonia and carbon dioxide for energy production. They commonly colonize the urogenital tract, where ammonia is readily excreted into the urine. In contrast, *Ureaplasma spp.* are not thought to be a normal constituent of the lung microbiota. They have been isolated from the respiratory tract in patients intubated for respiratory failure and from the airways of premature infants, where *Ureaplasma* colonization is associated with increased risk of bronchopulmonary dysplasia^{22,23}. Recent reports in lung transplant recipients have indicated that *Ureaplasma* species were causative agents in hyperammonemia as patients with fatal IHA had evidence of *U. parvum* or *U. urealyticum* detected by PCR in their lungs, bronchoalveolar lavage (BAL) or plasma while none of 20 lung transplant recipients with normal ammonia showed evidence of infection by PCR of BAL fluid or serum. Moreover, two patients with hyperammonemia and *Ureaplasma parvum* infection were treated with directed antibiotics with resolution of hyperammonemia and clearance of infection by PCR in the one patient where follow-up studies were performed. Additional causal evidence has been provided in experimental models which have confirmed that

Ureaplasma parvum can induce hyperammonemia in immunosuppressed mice^{24,25}. Of interest is a recent report implicating *Mycoplasma hominis* as a cause of hyperammonemia following lung transplantation, which is intrinsically resistant to macrolides but is usually susceptible to fluoroquinolones, as are *Ureaplasma* spp.²⁶.

In summary, hyperammonemia is a rare but devastating complication of HCT. Providers caring for these patients should be aware of the possible role of *Ureaplasma* species and consider testing and adding early empiric antibiotics (azithromycin and/or levofloxacin) to the treatment of IHA. Our case underscores the potential lifesaving response to early intervention with targeted antimicrobials and suggests the need for further study.

Figure Legend

Figure 1. Ammonia levels and treatment course of patient following matched unrelated HCT. Ammonia levels remained normal until day +80 when last tested.

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